

AMENDMENTS TO THE CLAIMS

1. (Original) An agent for inhibiting an excessive effect of NAD(P)H oxidase, which comprises a compound that does not substantially inhibit the effect of leukocyte NADPH oxidase but inhibits the effect of NAD(P)H oxidase in a tissue other than leukocyte.

2. (Original) The agent of claim 1, wherein the tissue other than leukocyte is a tissue of a vascular cell, the heart, the kidney, the retina, the microglia or a tumor cell.

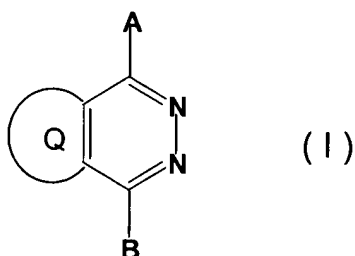
3. (Currently Amended) The agent of claim 1-~~or 2~~, wherein the excessive effect of NAD(P)H oxidase is caused by diabetes, hypertension, hyperlipidemia, obesity, smoking, heart failure, cardiac hypertrophy, ischemic heart diseases, angioplasty or ischemia-reperfusion in organ transplantation.

4. (Currently Amended) The agent of claim 1-~~or 2~~, wherein the excessive effect of NAD(P)H oxidase is caused by cancer or dementia.

5. (Currently Amended) The agent of claim 1-~~or 2~~, wherein the excessive effect of NAD(P)H oxidase is caused by intake of chemicals.

6. (Original) The agent of any one of claims 1 to 5, wherein the compound that does not substantially affect leukocyte NADPH oxidase but inhibits an excessive effect of NAD(P)H oxidase in a tissue other than leukocyte is a bicyclic pyridazine compound represented by the following formulas (I) to (VIII) or a pharmacologically acceptable salt thereof:

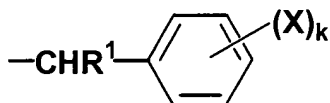
formula (I)



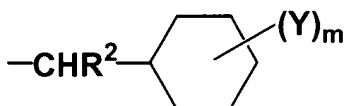
wherein A is C₃-C₆ alkyl, C₅-C₇ cycloalkyl, or phenyl, thienyl, furyl, thiazolyl, phenoxy, C₇-C₉ phenylalkyl, phenylthio, nitrogen-containing saturated ring group, pyridyl or imidazolyl, each optionally having one or more substituents selected from C₁-C₄ alkyl, C₁-C₄ alkoxy and halogen,

B is -NH-D

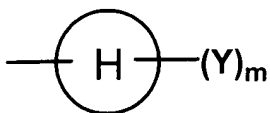
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wherein R¹ is hydrogen or C₁-C₄ alkyl, X is halogen, C₁-C₄ alkyl or C₁-C₄ alkoxy, and k is an integer of 0 to 3, when k is an integer of 2 or more, multiple Xs may be the same or different,



wherein R² is hydrogen or C₁-C₄ alkyl, Y is C₁-C₄ alkyl or C₁-C₄ alkoxy, and m is an integer of 0 to 6, when m is 2 or more, multiple Ys may be the same or different, and any two Ys may be joined to form optionally branched C₁-C₆ alkylene,

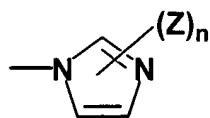


wherein ring H is C₅-C₇ cycloalkyl, and Y and m are as defined above,

-CHR³R⁴

wherein R³ is C₁-C₅ alkyl, and R⁴ is C₅-C₈ cycloalkyl or thienyl, or C₃-C₈ alkyl]

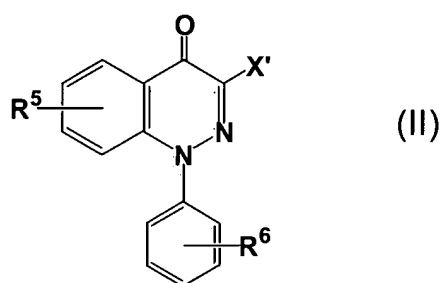
or



wherein Z is C₁-C₄ alkyl or phenyl, and n is an integer of 0 to 2, when n is 2, these Zs may be the same or different, and

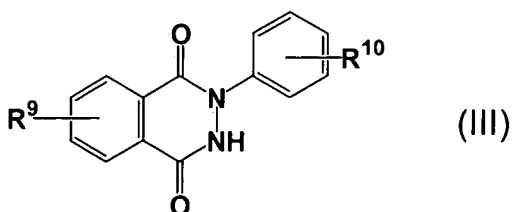
Q is a benzene ring, a furan ring or a thiophene ring optionally substituted by C₁-C₄ alkyl,

formula (II)



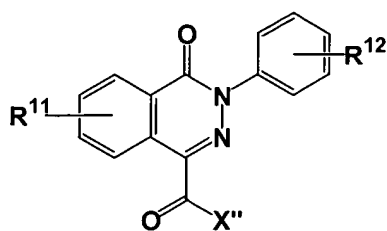
wherein R⁵ and R⁶ are each independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, cyano, nitro, amino, trifluoromethyl or carboxyl, and X' is -COOR⁷ (R⁷ is hydrogen or optionally substituted C₁-C₆ alkyl), -CONH₂, -CN, -COR⁸ (R⁸ is optionally substituted C₁-C₆ alkyl or optionally substituted aryl), -NH₂, -NO₂ or -OR⁷ (R⁷ is as defined above),

formula (III)

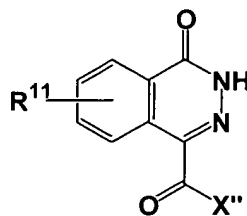


wherein R⁹ and R¹⁰ are each independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, cyano, nitro, amino, trifluoromethyl or carboxyl,

formulas (IV) and (V)



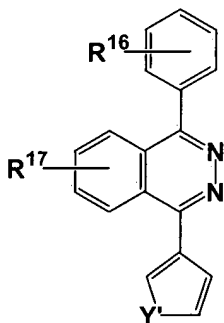
(IV)



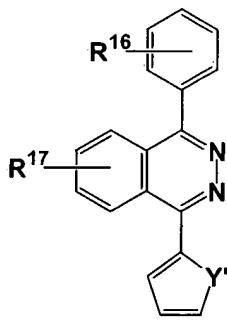
(V)

wherein R^{11} and R^{12} are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, cyano, nitro, amino, trifluoromethyl or carboxyl, and X'' is $-OR^{13}$ (R^{13} is hydrogen, C_1 - C_6 alkyl or aryl) or $-NR^{14}R^{15}$ (R^{14} and R^{15} are each independently hydrogen, C_1 - C_6 alkyl or aryl),

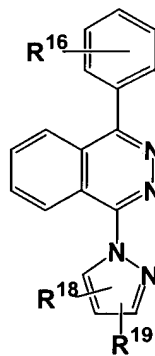
formulas (VI), (VII) and (VIII)



(VI)



(VII)



(VIII)

wherein R^{16} and R^{17} are each independently hydrogen, C_1 - C_6 alkyl, alkoxy, halogen, cyano, nitro, amino, trifluoromethyl or carboxyl, R^{18} and R^{19} are each independently hydrogen or C_1 - C_6 alkyl, and Y' is oxygen or sulfur.

7. (Currently Amended) A pharmaceutical composition for the diseases caused by an excessive effect of NAD(P)H oxidase, which comprises the agent of any one of claims 1 to 6 claim 1 as an active ingredient.

8. (Original) The pharmaceutical composition of claim 7, which is administered simultaneously with a hypolipidemic agent, an antihypertensive agent, a hypoglycemic agent, a vasodilator, an antiplatelet agent, an anticoagulant, a brain

protective agent, an anticancer agent, a diuretic agent, a cardiotonic agent, an analgesic agent, an antiedemic agent, a thrombolytic agent, an immunosuppressant, a steroid, a vitamin or an antioxidant, or administered separately therefrom, or administered sequentially therewith.

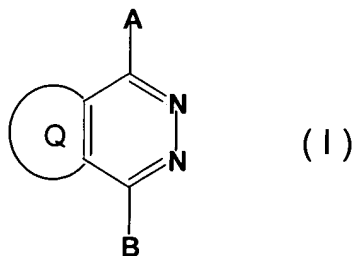
9. (New) The agent of claim 2, wherein the excessive effect of NAD(P)H oxidase is caused by diabetes, hypertension, hyperlipidemia, obesity, smoking, heart failure, cardiac hypertrophy, ischemic heart diseases, angioplasty or ischemia-reperfusion in organ transplantation.

10. (New) The agent of claim 2, wherein the excessive effect of NAD(P)H oxidase is caused by cancer or dementia.

11. (New) The agent of claim 2, wherein the excessive effect of NAD(P)H oxidase is caused by intake of chemicals.

12. (New) The agent of any one of claims 9 to 11, wherein the compound that does not substantially affect leukocyte NADPH oxidase but inhibits an excessive effect of NAD(P)H oxidase in a tissue other than leukocyte is a bicyclic pyridazine compound represented by the following formulas (I) to (VIII) or a pharmacologically acceptable salt thereof:

formula (I)

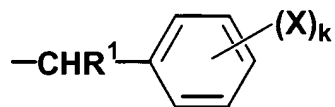


wherein A is C₃-C₆ alkyl, C₅-C₇ cycloalkyl, or phenyl, thienyl, furyl, thiazolyl, phenoxy, C₇-C₉ phenylalkyl, phenylthio, nitrogen-containing saturated ring group, pyridyl or

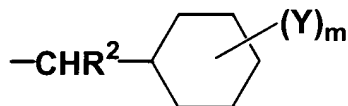
imidazolyl, each optionally having one or more substituents selected from C₁-C₄ alkyl, C₁-C₄ alkoxy and halogen,

B is -NH-D

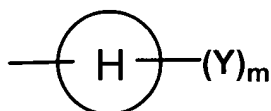
[D is



wherein R¹ is hydrogen or C₁-C₄ alkyl, X is halogen, C₁-C₄ alkyl or C₁-C₄ alkoxy, and k is an integer of 0 to 3, when k is an integer of 2 or more, multiple Xs may be the same or different,



wherein R² is hydrogen or C₁-C₄ alkyl, Y is C₁-C₄ alkyl or C₁-C₄ alkoxy, and m is an integer of 0 to 6, when m is 2 or more, multiple Ys may be the same or different, and any two Ys may be joined to form optionally branched C₁-C₆ alkylene,

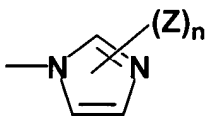


wherein ring H is C₅-C₇ cycloalkyl, and Y and m are as defined above,

-CHR³R⁴

wherein R³ is C₁-C₅ alkyl, and R⁴ is C₅-C₈ cycloalkyl or thienyl, or C₃-C₈ alkyl]

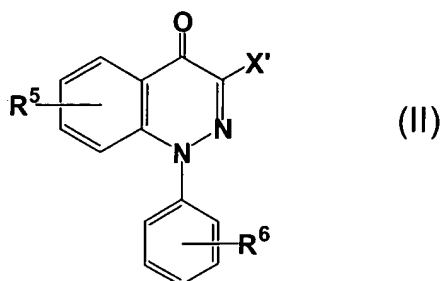
or



wherein Z is C₁-C₄ alkyl or phenyl, and n is an integer of 0 to 2, when n is 2, these Zs may be the same or different, and

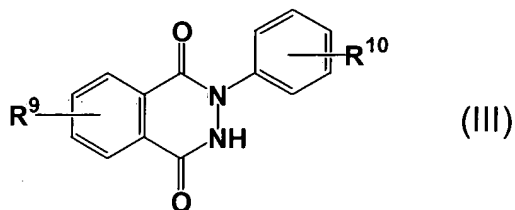
Q is a benzene ring, a furan ring or a thiophene ring optionally substituted by C₁-C₄ alkyl,

formula (II)



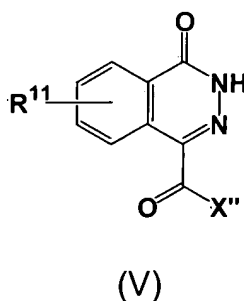
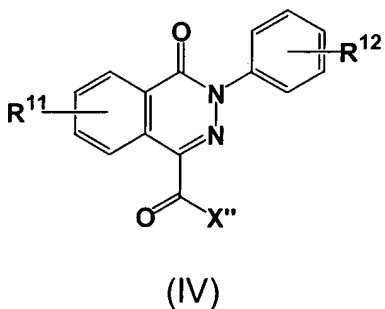
wherein R^5 and R^6 are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, cyano, nitro, amino, trifluoromethyl or carboxyl, and X' is $-COOR^7$ (R^7 is hydrogen or optionally substituted C_1 - C_6 alkyl), $-CONH_2$, $-CN$, $-COR^8$ (R^8 is optionally substituted C_1 - C_6 alkyl or optionally substituted aryl), $-NH_2$, $-NO_2$ or $-OR^7$ (R^7 is as defined above),

formula (III)



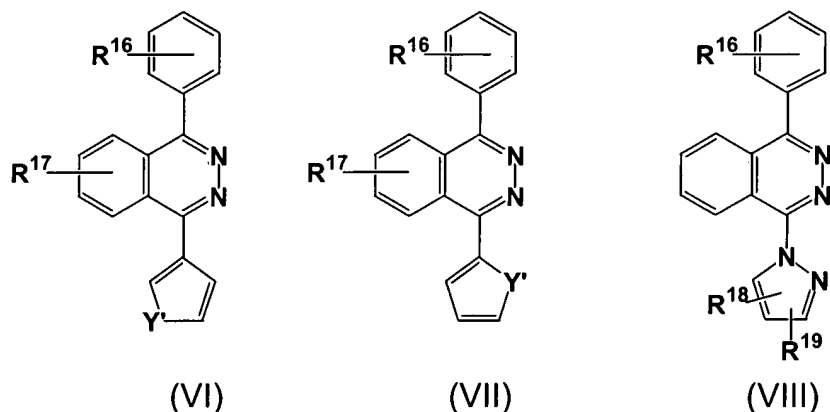
wherein R^9 and R^{10} are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, cyano, nitro, amino, trifluoromethyl or carboxyl,

formulas (IV) and (V)



wherein R^{11} and R^{12} are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, cyano, nitro, amino, trifluoromethyl or carboxyl, and X'' is $-OR^{13}$ (R^{13} is hydrogen, C_1 - C_6 alkyl or aryl) or $-NR^{14}R^{15}$ (R^{14} and R^{15} are each independently hydrogen, C_1 - C_6 alkyl or aryl),

formulas (VI), (VII) and (VIII)



wherein R¹⁶ and R¹⁷ are each independently hydrogen, C₁-C₆ alkyl, alkoxy, halogen, cyano, nitro, amino, trifluoromethyl or carboxyl, R¹⁸ and R¹⁹ are each independently hydrogen or C₁-C₆ alkyl, and Y' is oxygen or sulfur.

13. (New) A pharmaceutical composition for the diseases caused by an excessive effect of NAD(P)H oxidase, which comprises the agent of claim 6 as an active ingredient.

14. (New) The pharmaceutical composition of claim 13, which is administered simultaneously with a hypolipidemic agent, an antihypertensive agent, a hypoglycemic agent, a vasodilator, an antiplatelet agent, an anticoagulant, a brain protective agent, an anticancer agent, a diuretic agent, a cardiotonic agent, an analgesic agent, an antiedemic agent, a thrombolytic agent, an immunosuppressant, a steroid, a vitamin or an antioxidant, or administered separately therefrom, or administered sequentially therewith.